Management of Dyslipidemia in CKD

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CKD[1]

At least 3 month of either :
1-structural or functional abnormalities of the kidney that can lead to kidney failure or
2- GFR < 60 ml/min/1.73 m²

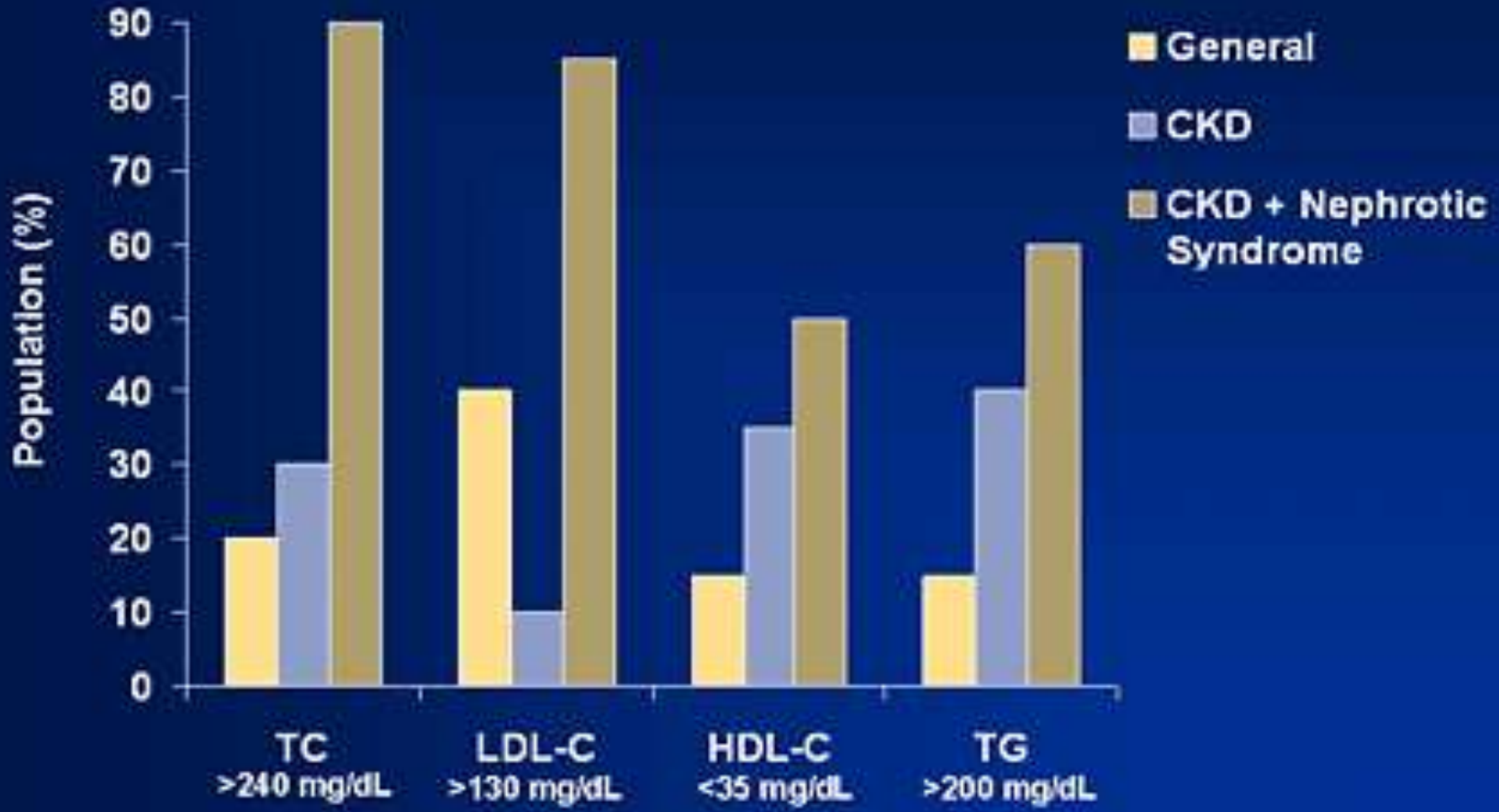
CKD stage	GFR (ml/min/1.73 m^2)
CKD1	≥ 90 (with renal damage or injury)
CKD2 (mild)	60-89
CKD3 (moderate)	30-59
CKD4 (sever)	15-29
CKD5 (ESRD)	<15, dialysis, or transplant

Dyslipidemia[1]

Any abnormality in plasma lipoprotein concentration or composition
is associated with an increased risk of atherosclerotic cardiovascular disease.

1-K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease

Prevalence of Dyslipidemia in patient with CKD



HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

Adapted from Kasiske BL. *Am J Kidney Dis* 1998;32(5 suppl 3):S142-S156

CVD IN CKD

- CVD accounts for 40-50% of all deaths in ESRD patients, with CVD mortality rates approximately 15 times that seen in the general population.

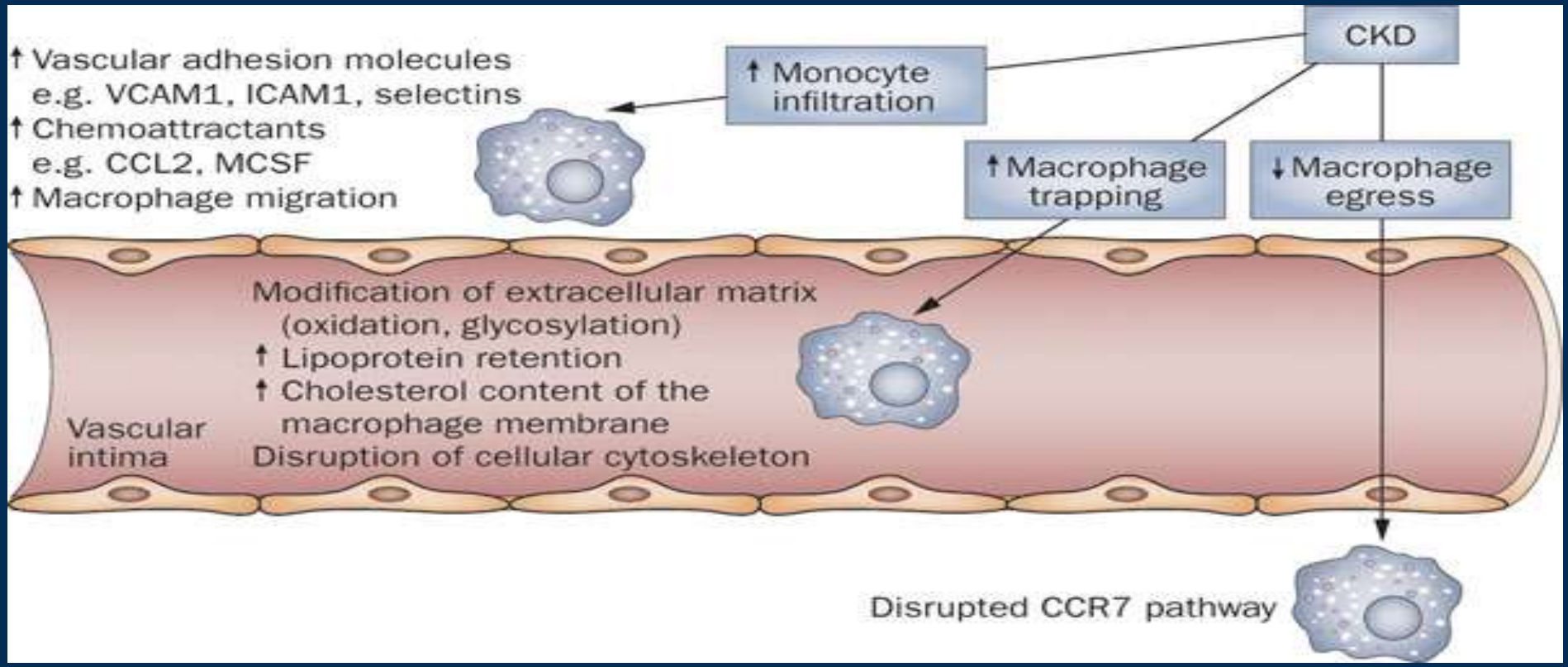
- **Risk factors for CVD in CKD including**
  proteinuria,
  inflammation,
  anemia,
  malnutrition,
  oxidative stress
  and uremic toxins.

- Meta-analyses of general population and high risk population cohorts found that both lower eGFR (<60 ml/min/1.73 m^2) and higher albuminuria (>10 mg/g creatinine) are predictors of total mortality and CVD mortality; furthermore, eGFR and albuminuria are independent of each other and of traditional CVD risk factors.

Estimated GFR > 60 ml/min/1.73 m^2 is not a risk factor for CVD or total mortality.

Mechanism Of Dyslipidemia In CKD

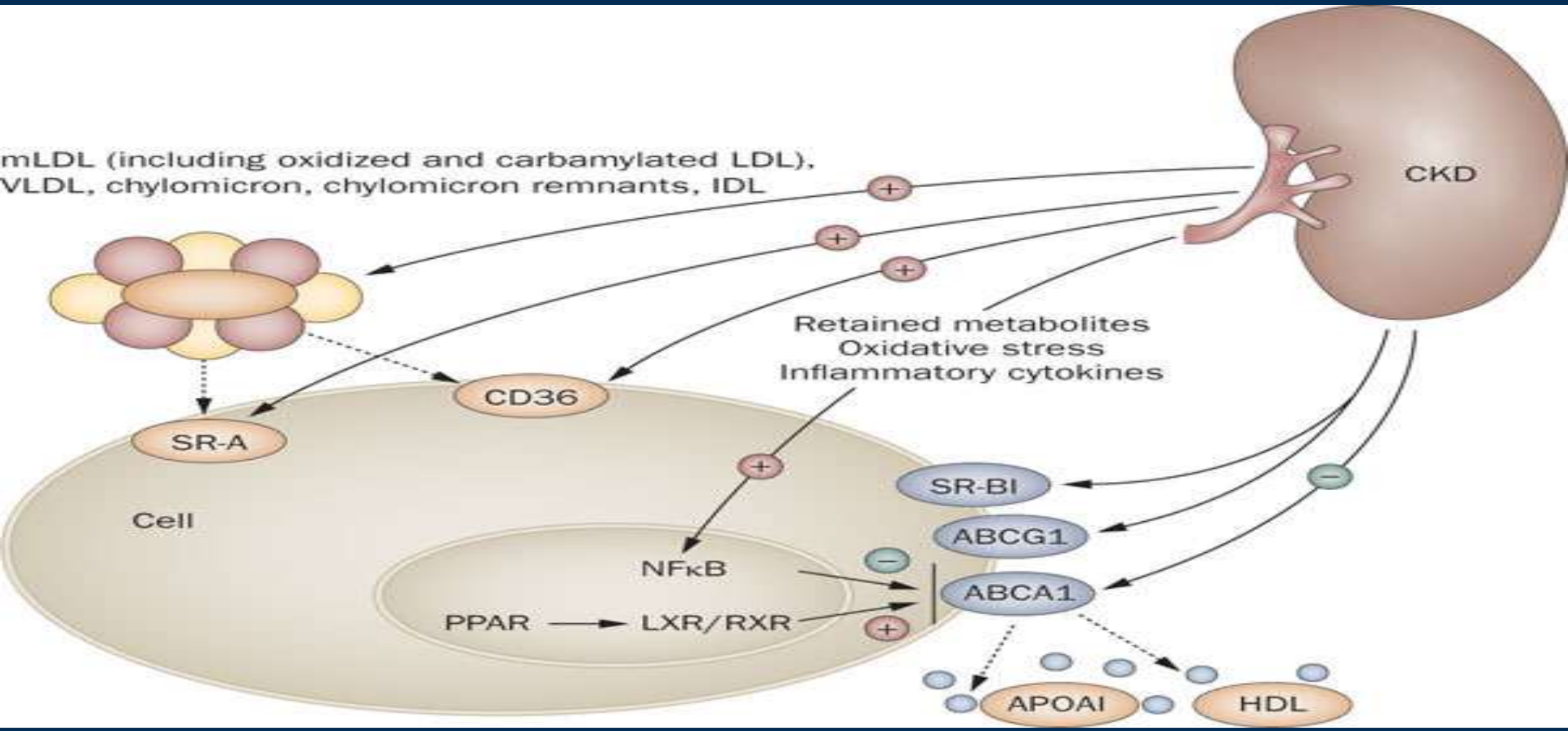
Potential pathways by which CKD modulates the accumulation of arterial macrophages



Kon, V. *et al.* (2010) Atherosclerosis in chronic kidney disease: the role of macrophages
Nat. Rev. Nephrol. doi:10.1038/nrneph.2010.157

Cont. Mechanism Of Dyslipidemia In CKD

Potential mechanisms by which CKD modulates macrophage lipid handling



Kon, V. *et al.* (2010) Atherosclerosis in chronic kidney disease: the role of macrophages *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2010.157

Effect of CKD on lipid levels

CKD causes
a **Profound Dysregulation of lipoprotien metabolism**

- **Decreased HDL-C**
- **Increased TGs**

Effect of CKD on lipoprotein composition

- lipoprotein particle size and composition is altered in CKD, with **increased small dense LDL** and decreased larger LDL particles in CKD subjects compared to controls.

- Small dense LDL is thought to be **more atherogenic** than larger LDL particles

KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease

OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

kidney INTERNATIONAL supplements

KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease

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NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

	Implications		
Grade*	**Patients**	**Clinicians**	**Policy-makers**
Level 1 'We recommend'	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 'We suggest'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

*The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m^2) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

1-Assessment Of lipid status in adults with CKD

Initial Evaluation of the lipid profile

- To establish the diagnosis of sever hypercholestrolemia or hypertriglyceridemia
- To potentially rule out a remediable (secondary cause) if dyslipidemia present

Table 2. **Secondary Causes of Dyslipidemia***

Medical Conditions
- The nephrotic syndrome
- Hypothyroidism
- Diabetes
- Excessive alcohol consumption
- Liver disease

Medications
- 13-cis-retinoic acid
- Anticonvulsants
- Highly active antiretroviral therapy
- Diuretics
- β-Blockers
- Androgens
- Oral contraceptives
- Corticosteroids
- Cyclosporine
- Sirolimus

- ✓ No direct evidence that measurement of lipid status will improve outcomes but fasting TG levels > 1000 mg/dl or LDL > 190 mg/dl should prompt consideration of further evaluation or specialist referral.

1.1: In adults with **newly identified CKD** (including those treated with chronic dialysis or kidney transplantation), we recommend evaluation with a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides). (1C)

1: we recommend. Most patients should receive the recommended course of action
C: Low quality of evidence

- ✓ Because the association between LDL cholesterol & adverse clinical outcome is weaker in person with CKD than in the general population, *the value of measuring LDL cholesterol to assess prognosis is uncertain.*

1.2: In adults with CKD (including those treated with chronic dialysis or kidney transplantation), follow-up measurement of lipid levels is not required for the majority of patients. (Not Graded)

Not Graded: was used, typically to provide guidance based on common sense or where the topic dose not allow adequate application of evidence.

- ✓ There is no direct evidence that routine follow-up of lipid levels improve clinical outcomes or adherence to lipid-lowering therapy

- ✓ However, the clinical benefits of lipid lowering treatment (including lower risk for myocardial infarction, stroke,& peripheral vascular events) are proportional to baseline coronary risk than baseline LDL cholesterol.

Higher Cardiovascular Risk
(rather than elevated LDL cholesterol levels) is now the Primary indication to initiate or adjust lipid-lowering treatment in CKD patients.

2: Pharmacological cholesterol-lowering treatment in adults

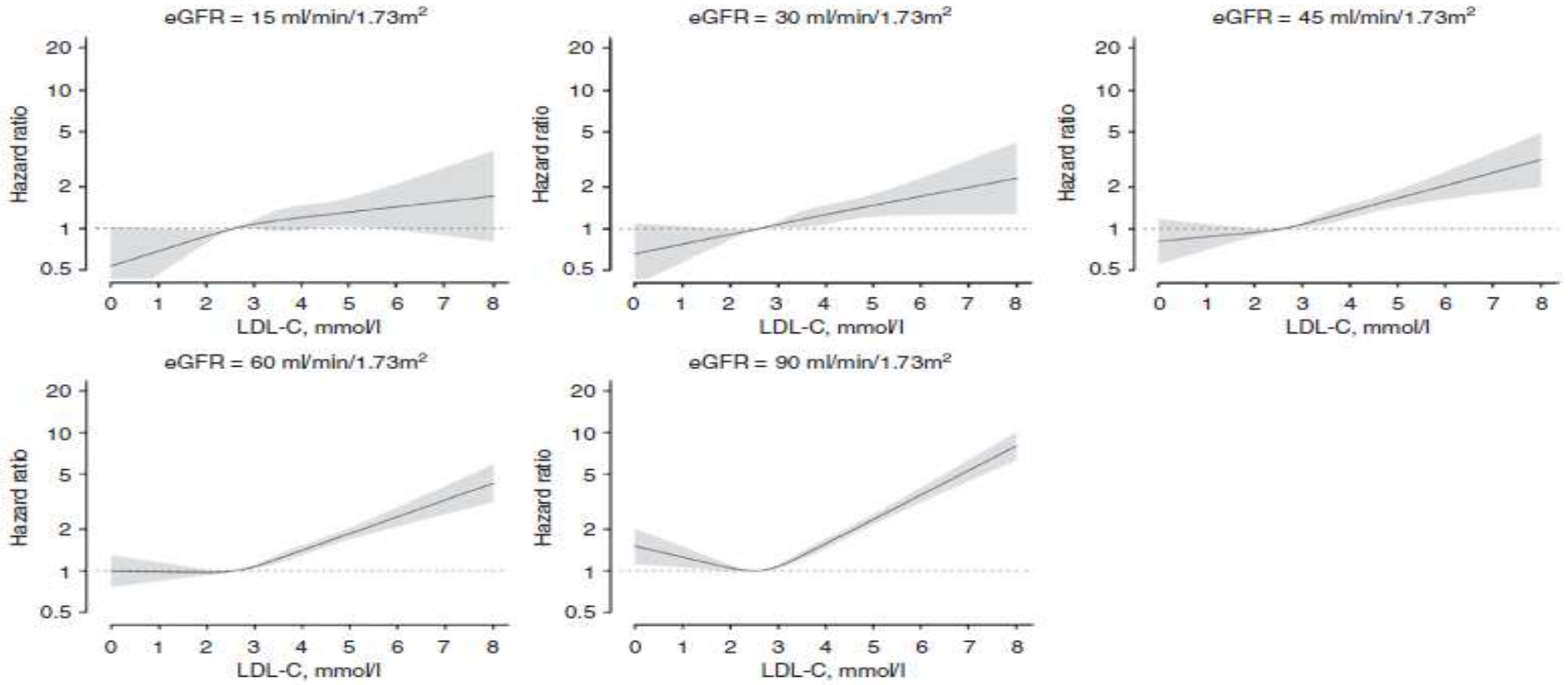
- To maximize the ratio of benefits to harm & cost, **Future coronary Risk** is considered an important potential determinants of the decision to prescribe cholesterol lowering treatment.

- In General Population, **LDL cholesterol** is widely used as a proxy for future risk because LDL cholesterol levels are strongly & independent association with risk for atherosclerotic events.

Which CKD should receive pharmacological cholesterol-lowering treatment?

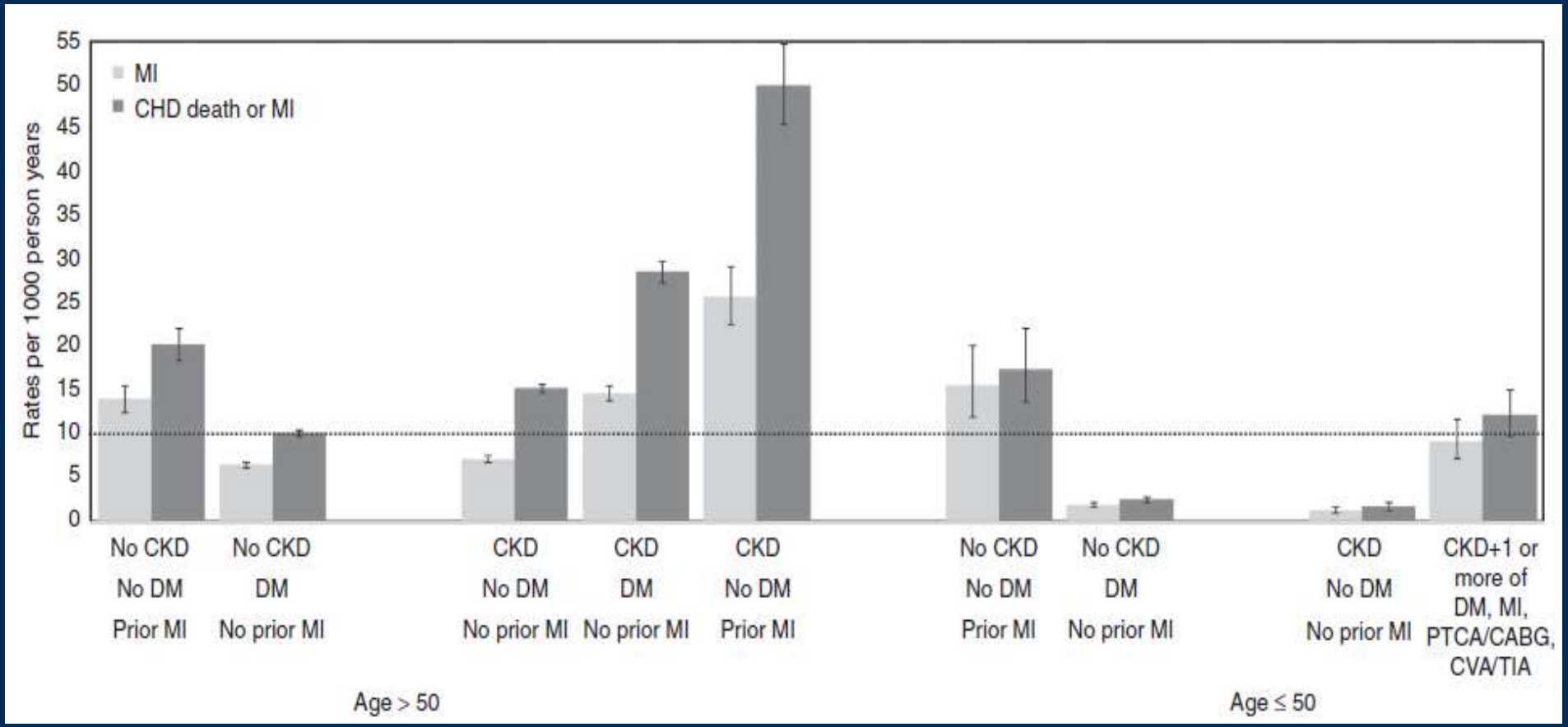
- **LDL-C is not suitable for assessing coronary risk in persons with CKD** although higher levels of LDL-C are associated with higher risk, dialysis patients with the lowest levels of LDL-C & total C are also at very high risk for all cause and C.V. Mortality likely because of confounding by inflammation & malnutrition.

❑ The magnitude of the excess risk associated with LDL-C levels decrease lower EGFRs



The weak & misleading association between LDL-C & coronary risk among those with lower levels of kidney function(who are at the highest absolute risk for coronary events) argues against the use of LDL-C for identifying CKD patients who should receive pharmacological cholesterol-lowering treatment & suggests focusing instead on **the absolute risk for coronary events.**

Coronary Risk:10-Year incidence of Coronary death or non fatal MI



CKD patients > 50 years (with or without DM or prior MI) consistently > 10%

Rate of coronary death or non-fatal MI (by age and eGFR)

	Rate (95% CI) of coronary death or non-fatal MI (per 1000 patient-years)		
	Overall	Male	Female
Age >40 years (eGFR G1-G4)	14.9 (14.6–15.3)	17.4 (16.9–17.9)	12.7 (12.3–13.1)
eGFR G3a-G4	19.3 (18.8–19.8)	23.4 (22.6–24.2)	16.4 (15.8–17.0)
eGFR G1-G2	9.7 (9.3–10.0)	12.0 (11.4–12.6)	6.7 (6.3, 7.2)
Age >50 years (eGFR G1-G4)	17.3 (17.0–17.7)	20.2 (19.6–20.8)	14.8 (14.3–15.3)
eGFR G3a-G4	19.9 (19.4–20.4)	24.3 (23.4–25.2)	16.9 (16.3–17.5)
eGFR G1-G2	12.9 (12.4–13.4)	15.2 (14.5–16.0)	9.7 (9.0–10.5)
Age 40–50 years (eGFR G1-G4)	3.2 (2.9–3.6)	4.7 (4.2–5.4)	1.6 (1.2–2.0)
eGFR G3a-G4	4.7 (3.7–6.0)	5.9 (4.3–8.1)	3.6 (2.5–5.3)
eGFR G1-G2	3.0 (2.6–3.3)	4.6 (4.0–5.3)	1.2 (0.9–1.6)

How should the dose of cholesterol lowering treatment be determined in CKD patients?

We should care about

- Decreased renal excretion
- Frequency of polypharmacy drug interaction
- Increased prevalence of co-morbidities in CKD population

Recommended doses (mg/d) of statins in adults with CKD

Statin	eGFR G1-G2	eGFR G3a-G5, including patients on dialysis or with a kidney transplant
Lovastatin	GP	nd
Fluvastatin	GP	80[1]
Atorvastatin	GP	20[2]
Rosuvastatin	GP	10[3]
Simvastatin/Ezetmibe	GP	20/10[4]
Pravastatin	GP	40
Simvastatin	GP	40
Pitavastatin	GP	2

All statins may not be available in all countries. Lower doses than those used in major trials of statins in CKD populations may be appropriate in Asian countries. Note that rosuvastatin 40 mg daily is not recommended for use in CKD 1-2 non-transplant patients, as it may increase the risk of adverse renal events. Cyclosporin inhibits the metabolism of certain statins resulting in higher blood levels. Data based on [1]ALERT, [2]4D, [3]AURORA, [4]SHARP. Abbreviations: eGFR, estimated glomerular filtration rate; GP, general population; nd, not done or not studied.

2.1.1: In adults aged ≥50 years with eGFR<60 ml/min/1.73 m2 but not treated with chronic dialysis or kidney transplantation (GFR categories G3a-G5), we **recommend treatment with a statin or statin/ezetimibe combination**. **(1A)**

1: we recommend. Most patients should receive the recommended course of action
A: High quality of evidence

2.1.2: In adults aged ≥50 years with CKD and eGFR≥60 ml/min/1.73m2 (GFR categories G1-G2) we **recommend treatment with a statin**. (1B)

1: we recommend. Most patients should receive the recommended course of action
B: Moderate quality of evidence

2.2: In adults aged 18–49 years with CKD but not treated with chronic dialysis or kidney transplantation, we **suggest** statin treatment in people with one or more of the following (2A):

-known coronary disease (MI or coronary revascularization)
-diabetes mellitus
-prior ischemic stroke
-estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10%

2: we Suggest :different choice will be appropriate for different patient
A: High quality of evidence

2.3.1: In adults with dialysis-dependent CKD, we suggest that statins or statin/ezetimibe combination not be initiated. **(2A)**

1- 4D Study (Die Deutsche Diabetes Dialyse Studie)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

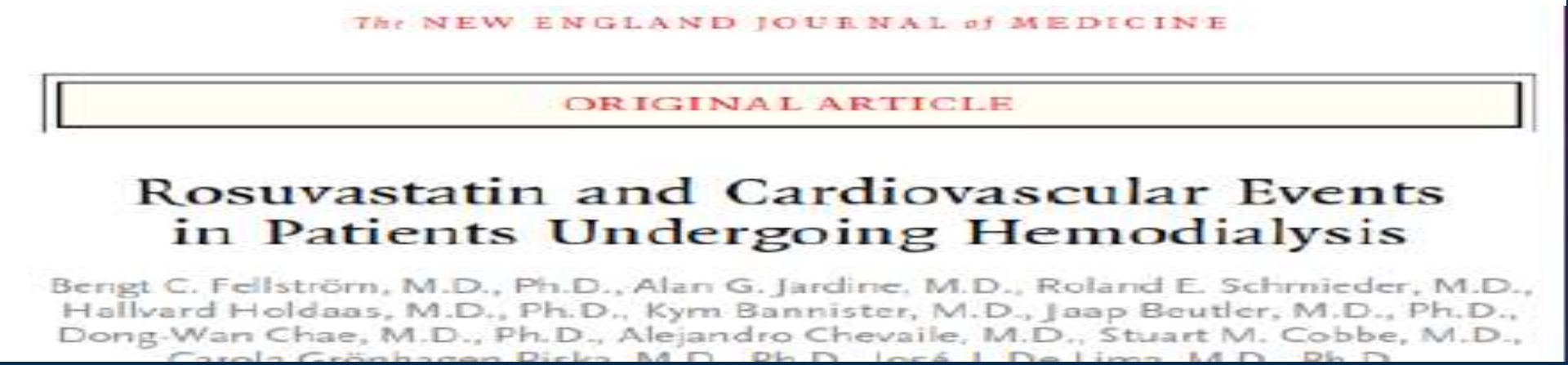
Atorvastatin in Patients with Type 2 Diabetes Mellitus Undergoing Hemodialysis

Christoph Wanner, M.D., Vera Krane, M.D., Winfried März, M.D., Manfred Olschewski, M.Sc., Johannes F.E. Mann, M.D., Günther Ruf, M.D., and Eberhard Ritz, M.D., for the German Diabetes and Dialysis Study Investigators*

The results of the 4D study, which to the surprise of many, demonstrated that:

- **lowering LDL-C with atorvastatin in hemodialysis (HD) patients with T2DM did not produce statistically significant reductions in the primary outcome measure (CVD,NF-MI,NF CVA).**
- **The study had strong impact on a recommendation for HD patients which stated that "treatment with a statin should not be initiated in patients with type 2 diabetes on maintenance HD therapy who do not have a specific cardiovascular indication for treatment.**

2-Aurora studie



The results of the Aurora study, was negative also like 4D studie, demonstrated that:

- **the combined endpoints of death from CV causes (NF-MI,NF CVA) was NOT REDUCED .**

- **Rosuvastatin DID NOT DECREASE the risk of individual components of the primary endpoints nor of ALL-Cause MORTALITY.**

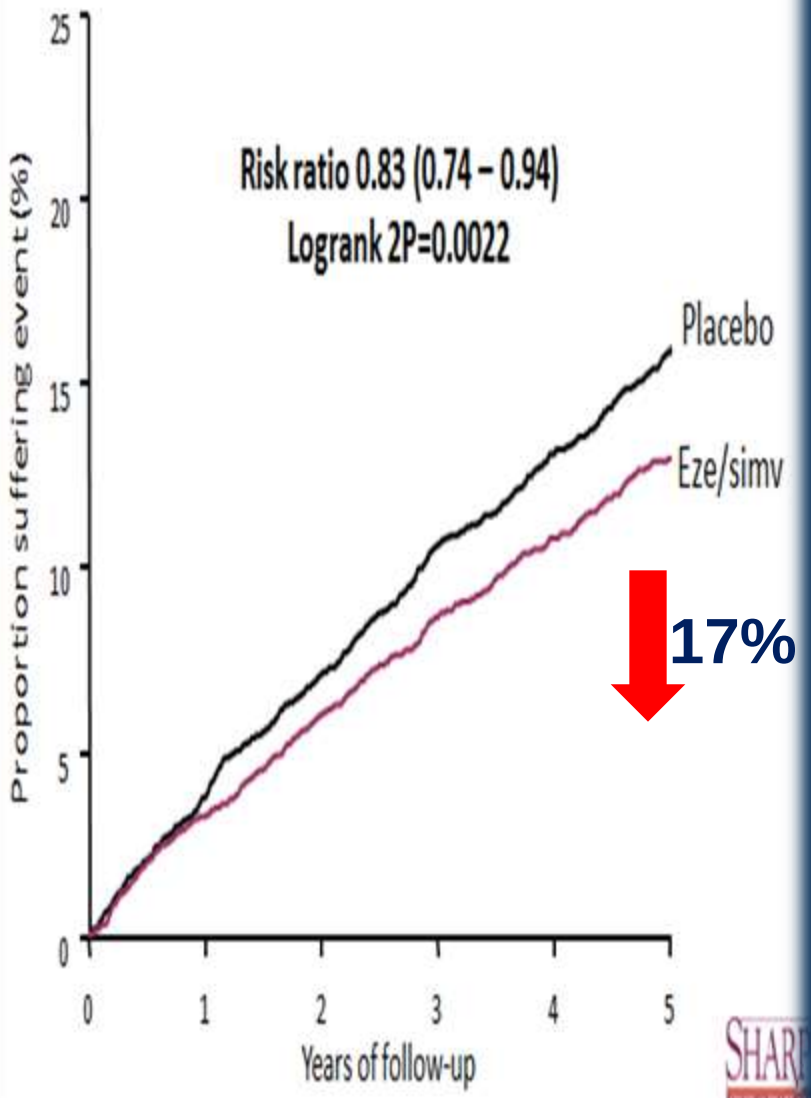
3-SHARP studie

The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial

*Colin Baigent, Martin J Landray, Christina Reith, Jonathan Emberson, David C Wheeler, Charles Tomson, Christoph Wanner, Vera Krane, Alan Cass, Jonathan Craig, Bruce Neal, Lixin Jiang, Lai Seong Hooi, Adeera Levin, Lawrence Agodoa, Mike Gaziano, Bertram Kasiske, Robert Walker, Ziad A Massy, Bo Feldt-Rasmussen, Udom Krairittichai, Vuddidhej Ophascharoensuk, Bengt Fellström, Hallvard Holdaas, Vladimir Tesar, Andrzej Wiecek, Diederick Grobbee, Dick de Zeeuw, Carola Grönhagen-Riska, Tanaji Dasgupta, David Lewis, William Herrington, Marion Mafham, William Majoni, Karl Wallendszus, Richard Grimm, Terje Pedersen, Jonathan Tobert, Jane Armitage, Alex Baxter, Christopher Bray, Yiping Chen, Zhengming Chen, Michael Hill, Carol Knott, Sarah Parish, David Simpson, Peter Sleight, Alan Young, Rory Collins, on behalf of the SHARP Investigators**

- International
- Double blind RCT
- 9270 patients with CKD
  - 3023 patients (33%) on dialysis
  - 6247 patients (67%) with mean eGFR ~ 27
- Simvastatin 20 daily + Ezetemibe 10 daily vs. Placebo
- 4.9 years

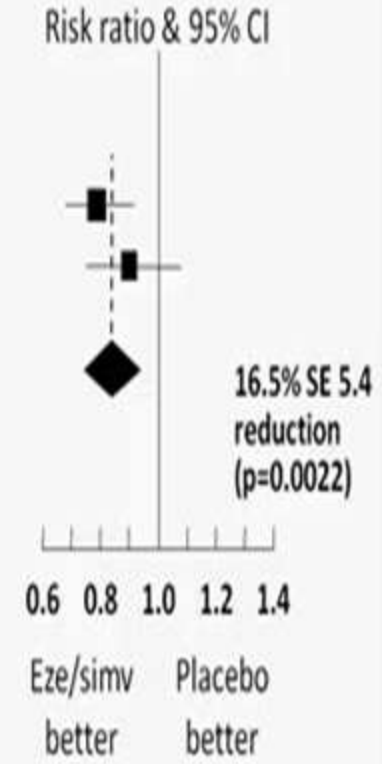
SHARP: Major Atherosclerotic Events



SHARP: Major Atherosclerotic Events by renal status at randomization

	Eze/simv (n=4650)	Placebo (n=4620)
Non-dialysis (n=6247)	296 (9.5%)	373 (11.9%)
Dialysis (n=3023)	230 (15.0%)	246 (16.5%)
Major atherosclerotic event	**526 (11.3%)**	**619 (13.4%)**

No significant heterogeneity between non-dialysis and dialysis patients (p=0.25)



- Combination therapy led to a **SIGNIFICANT 17% RR REDUCTION OF PRIMARY OUTCOME** of major atherosclerotic events (Coronary death, MI, Non-hemorrhagic CVA or any revascularization)
  - **BUT IN THE SUBGROUP OF 3023 DIALYSIS PATIENTS, THE RISK OF PRIMARY OUTCOME WAS NOT REDUCED.**

2.3.2: In patients **already receiving** statins or statin/ezetimibe combination at the time of dialysis initiation, we suggest that these agents be continued. (2C)

- 2141 (34%) of CKD patients who were not on dialysis at baseline but went on dialysis during the study
  - **Overall benefit** was observed

2.4: In adult kidney transplant recipients, we suggest treatment with a statin. (2B)

ALERT: Assessment of Fluvastatin in Renal Transplantation

Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial

*Hallvard Holdaas, Bengt Fellström, Alan G Jardine, Ingar Holme, Gudrun Nyberg, Per Fauchald, Carola Grönhagen-Riska, Søren Madsen, Hans-Hellmut Neumayer, Edward Cole, Bart Maes, Patrice Ambühl, Anders G Olsson, Anders Hartmann, Dag O Solbu, Terje R Pedersen, on behalf of the Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators**

ALERT: ASSESSMENT OF FLUVASTATIN IN RENAL TRANSPLANTATION

- 17% REDUCTION IN PRIMARY OUTCOME (Coronary death or Non-fatal MI) ~ NOT SIGNIFICANT
- **35% REDUCTION in cardiac death or definite non-fatal MI**
  - UNBLINDED EXTENSION STUDY: **SIGNIFICANT DECREASE IN ORIGINAL PRIMARY OUTCOME (after 6.7 years of follow up)**

Updated Recommendations for Lipid-lowering Therapy in CKD

- It is advisable to aggressively treat individuals who have an eGFR of 30 to 60 mL/min/1.73 m^2 and have known CHD and probably those without known coronary disease
  - On the basis of the findings from the Pravastatin Pooling Project
- It is reasonable to apply the currently accepted and footnoted guidelines (NCEP ATP-III) schema for treatment on the basis of LDL-C levels and LDL-C goals to those who have not yet reached end-stage renal disease (ESRD)

Updated Recommendations for Lipid-lowering Therapy in CKD

- It may be advisable to treat those with high risk for atherosclerotic cardiac events regardless of initial LDL level to achieve a marked (at least 30 to 40%) reduction in LDL
- A lower goal LDL of 70 mg/dL may be a reasonable therapeutic option in patients with CKD
- The increase in mortality in hemodialysis patients at lower cholesterol levels demands caution within this population

Updated Recommendations for Lipid-lowering Therapy in CKD

- It is reasonable but not mandatory to consider a reduced GFR, proteinuria, and perhaps microalbuminuria to be a “CHD-risk equivalent”
- Routine treatment of hemodialysis patients with diabetes may not be warranted
- Ezetimibe is a reasonable choice for a second-line lipid-lowering therapy in the CKD population and probably in kidney transplant recipients

Closing remarks:

- Coronary Risk is sufficiency high to justify prescription of statin in people aged ≥ 05 with non-dialysis dependent CKD or a Kidney transplant

- Coronary Risk in people aged <50 years with non-dialysis dependant CKD is lower, but the presence of additional CV risk factors may increase risk to justify statin prescription.

- Patients with dialysis-dependant CKD should NOT be initiated on lipid lowering therapy, given the lack of evidence that such treatment is beneficial.

- Physicians should be alert to the possibility of toxicity resulting from substances that increase blood levels of statins

Thank YOU